
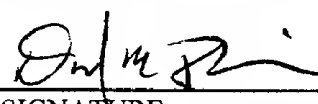


FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY DOCKET NUMBER JANS-0008 U.S. APPLICATION NO. (if known see 37 C.F.R. 1.51) <div style="font-size: 1.5em; font-weight: bold; text-align: center;">09/868991</div>
INTERNATIONAL APPLICATION NO. PCT/EP99/10257	INTERNATIONAL FILING DATE 20 December 1999	PRIORITY DATE CLAIMED 24 December 1998
TITLE OF INVENTION CONTROLLED RELEASE GALANTAMINE COMPOSITION		
APPLICANT(S) FOR DO/EO/US John Paul MCGEE; Paul Marie Victor GILIS; Marc Maurice Germain DE WEER; Valentin Florent Victor de CONDE; Herman Johannes Catherina de BRUIJN; Frederic Anne Rodolf VAN DYCKE		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) 35 U.S.C. 371(c)(4). 10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 		
Items 11. to 16. below concern other document(s) or information included:		
<ol style="list-style-type: none"> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information: <ul style="list-style-type: none"> - A copy of the Published PCT Application by WIPO under No. WO 00/38686, including the Search Report and references cited. - A copy of the International Preliminary Examination Report; Associate Power of Attorney. 		
EXPRESS MAIL Mailing Label No. EL 922206045 US Date of Deposit: June 21, 2001 I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 MAILER <u>John Hill</u> SIGNATURE <u></u>		

U.S. APPLICATION NO. (if known 37 CFR 1.53) 09/858991		INTERNATIONAL APPLICATION NO. PCT/EP99/10257		ATTORNEY DOCKET NUMBER JANS-0008	
17. <u> </u> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1) - (5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$1,000.00 International preliminary examination fee (37 CFR 1.482 not paid to USPTO but International Search Report has been prepared by the EPO or JPO..... \$860.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$710.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... \$690.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... \$100.00				<u>CALCULATIONS</u> <u>PTO USE ONLY</u>	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <u> </u> 20 <u> </u> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total claims	30 - 20 =	10	X \$18.00	\$180.00	
Independent Claims	1 - 3 =	0	x \$80.00	\$	
Multiple dependent claims(s) (if applicable)			+ \$270.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$1,040.00	
Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$	
SUBTOTAL =				\$1,040.00	
Processing fee of \$130.00 for furnishing the English translation later than <u> </u> 20 <u> </u> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	
TOTAL NATIONAL FEE =				\$1,040.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				+	
TOTAL FEES ENCLOSED =				\$1,040.00	
				Amount to be: refunded	\$
				charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ 1,040.00 to cover the above fee is enclosed. b. <u> </u> Please charge my Deposit Account No. 23-3050 in the amount of \$ <u> </u> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-3050. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: David N. Farsiou Woodcock Washburn Kurtz Mackiewicz & Norris LLP One Liberty Place - 46th Floor Philadelphia, PA 19103 (215) 568-3100			<div style="text-align: center;">  _____ SIGNATURE David N. Farsiou _____ NAME 44,104 _____ REGISTRATION NUMBER </div>		

DOCKET NO.: JANS-0008/JAB-1461

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

McGee et al.

U.S. Serial No.: Not yet assigned

Group Art Unit: Not yet assigned

Filed: Not yet assigned

Examiner: Not yet assigned

For: CONTROLLED RELEASE GALANTAMINE COMPOSITION

Assistant Commissioner of
Patents & Trademarks
Washington, DC 20231

PRELIMINARY AMENDMENT

Please amend the application, without prejudice, as follows.

In the Claims

Please amend claims 1, 4-5, 9, 11, 14-16, 19, 21, 23-25, 27-29 as follows:

1. (Amended) A controlled release formulation containing galantamine as the active ingredient, comprising particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, and a water soluble pharmaceutically acceptable excipient, said particles being coated by a release rate controlling membrane coating.

4. (Amended) A formulation according to claim 3 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s.
5. (Amended) A formulation according to claim 4 wherein the water soluble polymer is selected from
- (a) alkylcelluloses,
 - (b) hydroxyalkylcelluloses,
 - (c) hydroxyalkyl alkylcelluloses,
 - (d) carboxyalkylcelluloses,
 - (e) alkali metal salts of carboxyalkylcelluloses,
 - (f) carboxyalkylalkylcelluloses,
 - (g) carboxyalkylcellulose esters,
 - (h) starches,
 - (i) pectines,
 - (j) chitine derivatives,
 - (k) polysaccharides,
 - (l) polyacrylic acids and the salts thereof,
 - (m) polymethacrylic acids and the salts thereof, methacrylate copolymers,
 - (n) polyvinylalcohol,
 - (o) polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, or
 - (p) polyalkylene oxides.
9. (Amended) A formulation according to claim 8 wherein the inert spheres are 16-60 mesh sugar spheres.
11. (Amended) A formulation according to claim 10 wherein the water insoluble polymer is ethylcellulose and the plasticizer is selected from the group consisting of dibutyl sebacate, diethyl phthalate and triethyl citrate.

14. (Amended) A formulation according to claim 1 further comprising a topcoat comprising galantamine and water-soluble polymer.
15. (Amended) A formulation according to claim 14 capable of releasing from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours.
16. (Amended) A dosage form comprising a therapeutically effective amount of the controlled release formulation of claim 1.
19. (Amended) A dosage form according to claim 18 wherein said immediate release form comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, and a water soluble pharmaceutically acceptable excipient.
21. (Amended) A dosage form according to claim 18 wherein said immediate release form comprises said controlled release formulation, and a topcoat comprising galantamine and water-soluble polymer.
23. (Amended) A pharmaceutical package comprising a container, a formulation of galantamine as claimed in claim 1, and written matter specifying how said formulation should be administered.
24. (Amended) A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is acetylcholine esterase inhibitor-naïve, comprising 21-35 daily sequential dosage units of
- (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
 - (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,
 - (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
 - (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.

25. (Amended) A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is acetylcholine esterase inhibitor-tolerant, comprising daily dosage units comprising from 15 to 30 mg galantamine.
27. (Amended) A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.
28. (Amended) A method according to claim 27 wherein the related dementia is selected from the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit, hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.
29. (Amended) A method according to claim 27 wherein the adverse effects are selected from the group consisting of nausea, vomiting, sweating, restlessness, and insomnia.

Please add claim 30 as follows:

30. (New) A formulation according to claim 5 wherein the water soluble polymer is selected from the group consisting of methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylethylcellulose, sodium carboxymethylamylopectine, chitosan, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi

arabicum, guar gummi, xanthan gummi, polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide.

REMARKS

Claims 1-30 are presented. Claims 1, 4-5, 9, 11, 14-16, 19, 21, 23-25, 27-29 have been amended. Claim 30 has been added and no claims have been canceled.

The claims have been amended to remove multiple dependencies and to effect minor editorial amendments.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**" Entrance of the foregoing amendments and an early and favorable Action is respectfully requested.

Respectfully submitted,



David N. Farsiou
Registration No. 44,104

Date: 6/21/01

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098694-026904
T098694-026904

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend claims 1, 4-5, 9, 11, 14-16, 19, 21, 23-25, 27-29 as follows:

1. (Amended) A controlled release formulation containing galantamine as the active ingredient, [characterized in that it comprises] comprising particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, and a water soluble pharmaceutically acceptable excipient [and optionally other pharmaceutically acceptable excipients], said particles being coated by a release rate controlling membrane coating.
4. (Amended) A formulation according to claim 3 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s [when dissolved in a 2% aqueous solution at 20°C solution].
5. (Amended) A formulation according to claim 4 wherein the water soluble polymer is selected from [the group comprising]
 - [-] (a) alkylcelluloses [such as methylcellulose],
 - [-] (b) hydroxyalkylcelluloses [such as hydroxymethylcellulose, hydroxyethylcellulose,
 - hydroxypropylcellulose and hydroxybutylcellulose],
 - [-] (c) hydroxyalkyl alkylcelluloses [such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose],
 - [-] (d) carboxyalkylcelluloses [such as carboxymethylcellulose],
 - [-] (e) alkali metal salts of carboxyalkylcelluloses [such as sodium carboxymethylcellulose],

- [-] (f) carboxyalkylalkylcelluloses [such as carboxymethylethylcellulose],
- [-] (g) carboxyalkylcellulose esters,
- [-] (h) starches,
- [-] (i) pectines [such as sodium carboxymethylamylopectine],
- [-] (j) chitine derivatives [such as chitosan],
- [-] (k) polysaccharides [such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi],
- [-] (l) polyacrylic acids and the salts thereof,
- [-] (m) polymethacrylic acids and the salts thereof, methacrylate copolymers,
- [-] (n) polyvinylalcohol,
- [-] (o) polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, or
- [-] (p) polyalkylene oxides [such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide].

9. (Amended) A formulation according to claim 8 wherein the inert spheres are 16-60 mesh [(1,180-250 • m)] sugar spheres [(NF XVII, page 1989)].
11. (Amended) A formulation according to claim 10 wherein the water insoluble polymer is ethylcellulose and the plasticizer is selected from the group [comprising] consisting of dibutyl sebacate, diethyl phthalate and triethyl citrate.
14. (Amended) A formulation according to [any one of] claim[s] 1 [to 13] further comprising a topcoat comprising galantamine and water-soluble polymer.
15. (Amended) A formulation according to claim 14 capable of releasing [in USP buffer pH 6.8 at 37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50 rpm)] from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours.

16. (Amended) A dosage form comprising a therapeutically effective amount of the controlled release formulation of [any of] claim[s] 1 [to 15].
19. (Amended) A dosage form according to claim 18 wherein said immediate release form comprises particles [as described in claim 1 lacking the release rate controlling membrane] comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, and a water soluble pharmaceutically acceptable excipient.
21. (Amended) A dosage form according to claim 18 wherein said immediate release form comprises [a] said controlled release formulation [of claim 14] , and a topcoat comprising galantamine and water-soluble polymer.
23. (Amended) A pharmaceutical package [suitable for commercial sale] comprising a container, a formulation of galantamine as claimed in claim 1, and [associated with said package] written matter specifying how said formulation should be administered.
24. (Amended) A pharmaceutical package as claimed in claim 23 adapted for [titrating] treating a patient who is [‘]acetylcholine esterase inhibitor[’]-naïve, [characterized in that said package comprises] comprising 21-35 daily sequential dosage units of
- (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
 - (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,
 - (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
 - (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.
25. (Amended) A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is [‘]acetylcholine esterase inhibitor[’]-tolerant, [characterized in that said package comprises] comprising daily dosage units comprising from 15 to 30 mg galantamine.

27. (Amended) A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing [(avoiding)] the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.
28. (Amended) A method according to claim 27 wherein the related dementia [belongs to] is selected from the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit, hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.
29. (Amended) A method according to claim 27 wherein the adverse effects [belong to] are selected from the group [comprising] consisting of nausea, vomiting, sweating, restlessness, and insomnia.

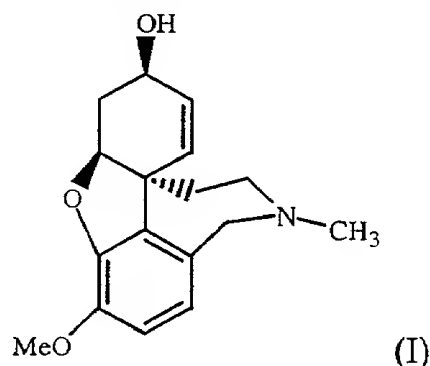
Please add claim 30 as follows:

30. (New) A formulation according to claim 5 wherein the water soluble polymer is selected from the group consisting of methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylethylcellulose, sodium carboxymethylamylopectine, chitosan, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi, xanthan gummi, polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide.

CONTROLLED RELEASE GALANTAMINE COMPOSITION

The present invention is concerned with controlled release compositions for oral
5 administration comprising galantamine ; and with processes of preparing such
controlled release compositions.

Galantamine (I), a tertiary alkaloid, has been isolated from the bulbs of the Caucasian
snowdrops *Galanthus woronowi* (Proskurnina, N. F. and Yakoleva, A. P. 1952,
10 Alkaloids of *Galanthus woronowi*. II. Isolation of a new alkaloid. (In Russian.) Zh.
Obschchei Khim. (J. Gen. Chem.) 22, 1899-1902). It has also been isolated from the
common snowdrop *Galanthus nivalis* (Boit, 1954).



The chemical name of galantamine is [4aS-(4a α , 6 β , 8aR*)]-4a, 5, 9, 10, 11, 12-
15 hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a, 3, 2-ef][2]benzazepin-6-ol ; both
the base compound and its hydrobromide are laevorotatory. Galantamine is a well-
known acetylcholinesterase inhibitor which is active at nicotinic receptor sites but not
on muscarinic receptor sites. It is capable of passing the blood-brain barrier in humans,
and presents no severe side effects in therapeutically effective dosages.

Galantamine has been used extensively as a curare reversal agent in anaesthetic practice
in Eastern bloc countries (cf. review by Paskow, 1986) and also experimentally in the
West (cf. Bretagne and Valetta, 1965; Wislicki, 1967; Consanitis, 1971).

Galantamine has been marketed by Waldheim (Sanochemia Gruppe) as NivalinTM in
25 Germany and Austria since the 1970s for indications such as facial neuralgia.

The use of galantamine or an analogue or a pharmaceutically acceptable acid addition
salt thereof for the preparation of a medicament for treating Alzheimer's Dementia
30 (AD) and related dementias has been described in EP-0,236,684 (US-4,663,318). This
patent only has a generic disclosure of possible dosage forms of galantamine.

CA-1,326,632 generically discloses slow release formulations of galantamine.

The use of galantamine for treating alcoholism and the administration via a transdermal therapeutic system (TTS) or patch is disclosed in EP-0,449,247 and WO-94/16707.

5 Similarly, the use of galantamine in the treatment of nicotine dependence using administration via a transdermal therapeutic system (TTS) or patch is disclosed in WO-94/16708. Treatment of nerve gas poisoning is disclosed in DE-4,342,174.

10 A number of applications by E. Snorrason disclose the use of galantamine, analogues thereof and pharmaceutically acceptable salts thereof for the preparation of medicaments for treating mania (US-5,336,675), chronic fatigue syndrome (CFS) (EP-0,515,302 ; US-5,312,817), the negative effects of benzodiazepine treatment (EP-0,515,301) and the treatment of schizophrenia (US-5,633,238). In these applications and patents, e.g. in US-5,312,817, a number of immediate release tablet
15 formulations of galantamine hydrobromide are given.

WO-97/47304 discloses fast-dissolving or immediate release tablets of galantamine prepared by direct compression. These and other art-known immediate release tablets are administered twice (b.i.d.) or thrice (t.i.d.) daily with an interval of 8 hours. The
20 plasma levels of the active ingredient typically raise sharply (early T_{max} and relatively high C_{max}) and decline rapidly (deep trough after about 6 to 8 hours).

Therapy with galantamine can be considered optimal when effective plasma levels are reached when required. In addition, peak values (C_{max}) should be as low and level as
25 possible so as to reduce the incidence and severity of possible side effects. The foregoing requirements not only apply upon single dose administration, but also upon repeated dose administration (until a steady-state condition is reached). In particular, when treating a patient suffering from Alzheimer's Disease, optimum efficacy is expected when effective plasma levels are maintained during daytime; during nighttime
30 galantamine plasma levels probably may be lower. For the treatment of other conditions, for example for treating sleep disordered breathing such as snoring and apnoea (WO-97/22339), one may wish to attain the reverse situation, namely to have effective plasma levels during the night, and lower levels during daytime. For the benefit of the patient and the caretakers, a pharmaceutical dosage form that has to be
35 administered once daily only and yields effective plasma levels for eight hours (nighttime) to 16 hours (daytime) would be highly desirable.

The present invention relates to a controlled release formulation containing galantamine

as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating.

- 5 Dosage forms comprising a therapeutically effective amount of said controlled release formulations can be administered orally to a patient once daily. In preferred dosage forms, part of the galantamine is present in an immediate release form, for example, as particles lacking a release rate controlling membrane coating, or as immediate release minitabets, or as as a topcoat on the controlled release formulation.

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Preferably, the formulations according to the present invention comprise galantamine in the form of galantamine hydrobromide (1:1).

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The water soluble excipient can conveniently be a film forming polymer. Useful water soluble film forming polymers are polymers that have an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water soluble polymer can be selected from the group comprising

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- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose,
- hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethyl-cellulose,
- carboxyalkyl alkylcelluloses such as carboxymethyl ethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate

- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

Preferred water-soluble polymers are for example hydroxypropyl methylcellulose (Methocel®, Pharmacoat®), polymethacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®), or a polyvidone. Especially preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). Preferably hydroxypropyl methylcellulose with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s. The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s. An equally preferred type of HPMC is admixed with polyethylene glycol 400, commercially available from Colorcon (UK) as Opadry™ OY-7240 clear.

The weight-by-weight ratio of drug : polymer is in the range of 17 : 1 to 1 : 5, preferably 10 : 1 to 1 : 3. In the case of (galantamine.HBr) : (HPMC 2910 5 mPa.s), said ratio may range from about 10 : 1 to about 1 : 3, and optimally is from 7 : 1 to 1 : 2. The weight-by-weight ratio of galantamine.HBr to other water-soluble polymers may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations.

In particular the present invention is concerned with particles which comprise (a) a central, rounded or spherical core, (b) a layer or a coating film of a water-soluble polymer and galantamine hydrobromide (1:1), (c) optionally a seal-coating polymer layer and (d) a release rate controlling membrane coating. The core has a diameter of about 250 to about 1,180 μm (16-60 mesh), preferably of about 600 to about 1,180 μm (16-30 mesh).

Pellets, beads or cores of the dimensions mentioned herein can be obtained by sieving through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Materials suitable for use as cores in the particles according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions (about 16-60 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

A particularly preferred material suitable for use as cores in the particles according to the present invention is represented by 16-60 mesh sugar spheres (USP 22 / NF XVII, p. 1989) which consist of 62.5% - 91.5% (w/w) sucrose, the remainder being starch and possibly also dextrans, and which are pharmaceutically inert or neutral. Consequently, these cores are also known in the art as neutral pellets.

Depending on the weight-by-weight ratio of drug : polymer, the water-soluble polymer and galantamine are herein said to form either a layer (ratio > 10 : 1) or a coat or coating film (ratio < 10 : 1).

As an alternative to the drug layered or drug coated inert pellets described thus far, suitable particles comprising glantamine may also be formed by granules or by spheroids (spherical granules) prepared according to art-known methods of granulation and spheronization.

5

The release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer. Said polymer is ethylcellulose and the plasticizer is selected from the group comprising dibutyl sebacate, diethyl phthalate and triethyl citrate. It is useful to modify the properties of the water-insoluble polymer by the addition of particular amounts of a water-soluble polymer as described hereinbefore, preferably HPMC. The addition of the water-soluble polymer is especially useful to increase the onset of action. For the particles according to the present invention, the ratio ethylcellulose : HPMC can vary from 100 : 0 to about 70 : 30, in particular from about 80 : 20 to about 72.5 : 27.5, more in particular from about 75 : 25 to about 72.5 : 27.5. The release rate controlling membrane coating may be applied to the drug coated cores in an aqueous dispersion (Aquacoat™, Surelease™), or as a solution in an organic solvent system. A useful organic system comprises an alcohol, *e.g.* methanol or ethanol, and optionally a chlorinated hydrocarbon such as for example dichloromethane.

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The weight of the release rate controlling membrane coating ranges from 3 % to 15 % of the uncoated particle, in particular from about 4% to about 12 %. The rate of release of the active ingredient from the particles is approximately inversely proportional with the thickness of the release rate controlling membrane coating.

25

A seal coat lies optionally between the drug core and the release rate controlling membrane coating. The seal coating polymer layer is applied to the drug coated cores to prevent sticking of the particles during the process and to prevent migration of the drug into the the release rate controlling membrane. Preferably, a thin layer of HPMC 2910 5 mPa.s and polyethylene glycol (PEG), in particular polyethylene glycol 400 is used as a seal coating polymer layer.

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In addition, the particles according to the present invention may further contain various additives such as thickening agents, lubricants, surfactants, preservatives, complexing and chelating agents, electrolytes or other active ingredients.

The particles can be filled in hard-gelatin capsules such that a therapeutically effective amount of, for example, 8 to 32 mg of the active ingredient is available per dosage

form. An advantageous pharmacokinetic profile (fast onset, level peak and trough values) is obtained when from 70 to 80 % of the galantamine is comprised within the controlled release particles and the remaining 20 to 30 % of the galantamine is comprised in an immediate release form, preferably the controlled release particle amount to 75 % of the galantamine and the immediate release form to 25 %.

In order to achieve the desired pharmacokinetic, the dosage forms may be filled with particles that release the active ingredient at different rates, at least one kind that releases the active ingredient slowly, and at least one kind that releases the active ingredient more rapidly, in particular one kind that releases the active ingredient immediately, e.g. particles as described that lack the release rate controlling membrane. The different particles may be filled consecutively in the capsules, or they may be premixed and the thus obtained premix may be filled into the capsules (taking into account possible segregation).

Alternatively, the controlled release particles of the present invention may further comprise a top-coat of a water-soluble polymer as described hereinbefore and galantamine which is released practically immediately upon ingestion and thus ensures a rapid onset of action.

Another alternative solution for providing a dosage form with a pharmacokinetic profile as outlined, namely with a fast onset, level peak and trough values, comprises filling a capsule with controlled release particles as described hereinbefore (70 to 80 %, preferably 75 % of the galantamine dose) together with one or more minitablets which comprise the remaining 20 to 30 %, preferably 25 % of galantamine. Suitable immediate release tablet formulations of galantamine have been described previously in WO-97/47304.

The present invention also relates to processes of preparing formulations as described hereinbefore comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.

The particles according to the present invention are conveniently prepared in the following manner. A drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of galantamine.HBr and a water-soluble polymer. A suitable solvent system comprises purified water or an alcohol, preferably ethanol

which may be denatured, for example, with butanone. The amounts of solids, *i.e.* galantamine.HBr and water-soluble polymer, in the drug coating solution may range from 10 to 30% (w/w) and preferably is about 25 %. The solution is preferably stirred during the coating process.

5

The drug coating process (on an industrial scale) is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30 or GPCG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Laboratory scale process development can be performed on a Glatt type WSG-1 with a 6 inch Wurster bottom insert. Obviously the process parameters depend on the equipment used.

10

The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the particles grow larger.

15

The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.

20

Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum pellet circulation is obtained. Too low an air volume will cause insufficient fluidization of the pellets; too high an air volume will interfere with the pellet circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

30

The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50°C to about 55°C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the pellets resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated pellets increases,

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drug dissolution may decrease significantly to unacceptable levels. Obviously, the optimum process temperature will further depend on the equipment used, the nature of the core, the batch volume, the solvent and the spraying rate.

- 5 Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to yield very reproducible results.

- 10 In order to decrease residual solvent levels in the pellets following application of the rate controlling membrane from an organic solution, the pellets can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60°C to about 90°C, preferably about 80°C, a reduced pressure ranging from about 150-400 mbar (15-40 kPa), preferably 200-300 mbar (20-30 kPa), for at least 24 hours, preferably about 36 hours.
- 15 The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

- 20 The seal coat layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert or in a powder coater. The seal coating solution can be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone. The amount of seal coating polymer in the seal coating spraying solution may range from 5 to 10% (w/w) and preferably is about 6.6%. The seal coating spraying solution is advantageously
- 25 stirred during the seal coating process. Appropriate conditions are described in more detail in the example hereinafter.

- 30 A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

- 35 The release rate controlling membrane coating polymer layer is applied to the drug (or seal) coated cores in a fluidized bed granulator with Wurster bottom spray insert. The release rate controlling membrane coating suspension or solution can be prepared by suspending or dissolving an appropriate amount of a release rate controlling membrane coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone, dichloromethane which may be admixed with an alcohol, preferably methanol or

ethanol. The amount of release rate controlling membrane coating polymer in the spraying suspension or solution may range from 5 to 40% (w/w) and preferably is about 30%. The release rate controlling membrane coating spraying suspension or solution is advantageously stirred during the spraying process. The parameter setting for
5 conducting this last step is essentially similar to that used in the previous coating processes. Appropriate conditions are described in more detail in the example hereinafter.

All coating processes are preferably conducted under an inert atmosphere of *e.g.*
10 nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

The particles may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously
15 prevent development of electrostatic charges.

Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.
20

Dosage forms according to the present invention having an advantageous pharmacokinetic profile as outlined, namely a fast onset and level peak and trough values, are capable of releasing in 500 ml USP buffer (pH 6.8) at 37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50 rpm) from 20 to 40 % of the
25 total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours. Said dosage forms provide a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.
30

The formulations according to the present invention deliver a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.

35 The present invention also concerns pharmaceutical packages suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.

Said pharmaceutical packages may be adapted for titrating a patient who is 'acetylcholine esterase inhibitor'-naïve, i.e. a patient who has not been exposed to an acetylcholine esterase inhibitor before and who should start with small, well-tolerated doses before being exposed to ever higher doses until the optimal dose is reached. Said packages typically comprises 21-35 daily sequential dosage units of

- (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
- (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,
- (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
- (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.

Alternatively, the pharmaceutical packages may be adapted for treating a patient who is 'acetylcholine esterase inhibitor'-tolerant, i.e. a patient who has been exposed to an acetylcholine esterase inhibitor before and who tolerates an optimal dose. Said packages typically comprises daily dosage units comprising from 15 to 30 mg galantamine.

A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.

The related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.

The adverse effects belong to the group comprising nausea, vomiting, sweating, restlessness, and insomnia.

Experimental partExample 1 : 8 mg galantamine CR oral capsule (F1)*Ingredients :*

	galantamine hydrobromide	10.253 mg (8 mg galantamine base)	
5	sugar spheres (18-20 mesh)	63.283 mg	
	HPMC 2910 5 mPa.s	1.465 mg	
	purified water	37.105 µl	*
	HPMC 2910 5 mPa.s	1.500 mg	
	polyethylene glycol 400	0.150 mg	
10	purified water	23.350 µl	*
	ethylcellulose aqueous dispersion	10.220 mg	(30 %)
	dibutyl sebacate	0.736 mg	
	purified water	10.220 µl	*

capsule nr. 4

15 * : these ingredients do not occur in the end product

Preparation :

a) Drug coat suspension

Galantamine hydrobromide (123 g) was suspended in 297 ml purified water and heated to 70 -80 °C. HPMC 2910 5 mPa.s (17.58 g) was dissolved in the heated suspension

20 whilst stirring.

b) Seal coat solution

Purified water (93.4 g) was heated to 70 - 80°C and HPMC 2910 5 mPa.s (18 g) and polyethylene glycol 400 (1.8 g) were dissolved therein. The solution was then further diluted with purified water (186.8 g).

25 c) Release rate controlling membrane coat dispersion

To a gently stirred aqueous dispersion of ethylcellulose (122.6 g ; 30 %) was added dibutyl sebacate (8.832 g). The dispersion was diluted with purified water (122.6 g).

d) Coating process

A fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres (759.4 g). The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug coat suspension was sprayed on the spheres moving in the apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16 -0.4 MPa). When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The

coated spheres were then seal coated with the sealcoat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

- 5 The fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16 -0.4 MPa). After drying for about 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

e) drying and curing process

- 15 In order to remove agglomerates, the coated spheres were sieved using a sieve having a mesh width of 1.2 mm. The particles were placed in a drying oven at 60°C during 2 hours so as to cure the release rate controlling membrane.

f) capsule filling

- 20 The particles were filled into hard-gelatin capsules (size 4) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg. Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 87.6 mg particles, equivalent to about 8 mg galantamine.

25 Example 2 : 8 mg galantamine CR oral capsule (F2)

Ingredients :

	galantamine hydrobromide	10.253 mg (8 mg galantamine base)	
	sugar spheres (18-20 mesh)	63.283 mg	
	HPMC 2910 5 mPa.s	1.465 mg	
30	purified water	37.105 µl	*
	HPMC 2910 5 mPa.s	1.500 mg	
	polyethylene glycol 400	0.150 mg	
	purified water	23.350 µl	*
	ethylcellulose aqueous dispersion	25.550 mg	(30 %)
35	dibutyl sebacate	1.840 mg	
	purified water	25.550 µl	*
	capsule nr. 4		

* : these ingredients do not occur in the end product

Preparation :

The preparation was identical to that described in Example 1 except for the preparation
5 of the release rate controlling membrane dispersion.

c) Release rate controlling membrane coat dispersion

To a gently stirred aqueous dispersion of ethylcellulose (306.6 g ; 30 %) was added
10 dibutyl sebacate (22.08 g). The dispersion was diluted with purified water (306.6 g).

Example 3: Bioavailability

The bioavailability of a single oral administration of the two controlled release
formulations of examples 1 and 2 was compared with that of an immediate release
15 tablet (F3) [WO-97/47304] comprising 4 mg galantamine which was administered
twice daily with an interval of 8 hours. Galantamine plasma levels in healthy
volunteers (12) were determined by HPLC and the mean values calculated from the
individual measurements are reported in the following table.

time (h)	F1	F2	F3
0	nd	nd	nd
0.5	1.6	nd	16.4
1	7.3	nd	24.1
1.5	11.5	nd	20.3
2	16.3	1.8	18.3
3	23.8	3.7	16.9
4	26.7	6.3	14.5
6	25.2	9.5	11.3
8	22.5	10.5	9.3
8.5			18
9			24.5
9.5			25.5
10	18.6	11.1	23.7
11			22.7
12	15.1	12.0	19.3
14	13.4	12.4	15.2
16	10.8	11.7	12.7
24	6.0	8.8	6.6

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time (h)	F1	F2	F3
30	3.5	6.1	3.5
36	2.0	4.3	2.0
48	nd	1.6	nd

nd : not detectable (< 1 ng/ml)

Example 4 : oral capsule (F4) comprising 8 mg galantamine
(75 % CR pellets and 25 % IR tablet)

Ingredients :

5	sugar spheres (18-20 mesh)	63.482 mg	
	galantamine hydrobromide	7.69 mg (6 mg galantamine base)	
	HPMC 2910 5 mPa.s	0.641 mg	
	purified water	42.932 µl	*
	HPMC 2910 5 mPa.s	1.436 mg	
10	polyethylene glycol 400	0.145 mg	
	methylene chloride	12.385 µl	*
	ethanol 96 % (v/v)	10.858 mg	*
	HPMC 2910 5 mPa.s	1.101 mg	
	ethylcellulose 20 mPa.s	3.308 mg	
15	diethyl phthalate	0.881 mg	
	methylene chloride	31.077 µl	*
	ethanol 96 % (v/v)	27.244 mg	*
	galantamine hydrobromide	2.563 mg (2 mg galantamine base)	
	spray-dried mixture of lactose monohydrate		
20	and microcrystalline cellulose (75:25)	49.302 mg	
	colloidal anhydrous silica	0.11 mg	
	croscopolvidone	2.750 mg	
	magnesium stearate	0.275 mg	
25	* : these ingredients do not occur in the end product		

Preparation :

a) Drug layer suspension

Galantamine hydrobromide was suspended in purified water and heated to 70 -80 °C.

30 HPMC 2910 5 mPa.s was dissolved in the heated suspension whilst stirring.

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b) Seal coat solution

Methylene chloride and ethanol were mixed together and polyethylene glycol and HPMC 2910 5 mPa.s were dissolved therein.

5 c) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, HPMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

d) Layering and coating process

- 10 A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug layer suspension was sprayed on the spheres moving in the apparatus. When the spraying process was completed, the layered
- 15 spheres were dried by further supplying dry air of 60°C for about 2 minutes. The layered spheres were then seal coated with the seal coat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.
- 20 The fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the apparatus. After drying for about
- 25 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature, sieved and filled into a stainless steel drum.

e) immediate release minitab

- Galantamine hydrobromide, spray-dried mixture of lactose monohydrate
- 30 and microcrystalline cellulose (75:25), colloidal anhydrous silica, croscopolyvidone and magnesium stearate were mixed in a planetary mixer and compressed in a tableting machine, thus preparing minitabets of 55 mg weight.

f) capsule filling

- 35 The coated spheres and the immediate release minitab were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg. Germany).

Example 5 : galantamine oral capsules (F5, F6, F7, F8)

(75 % CR pellets and 25 % IR topcoat)

Ingredients :

	sugar spheres (18-20 mesh)	63.624 mg	
5	galantamine hydrobromide	7.69 mg (6 mg galantamine base)	
	HPMC 2910 5 mPa.s and PEG 400	12.687 mg (Opadry™ OY-7240 Clear, Colorcon)	
	purified water	267.693 µl	*
	HPMC 2910 5 mPa.s	1.260 mg	
	ethylcellulose 20 mPa.s	3.780 mg	
10	diethyl phthalate	1.008 mg	
	methylene chloride	46.772 µl	*
	ethanol 96 % (v/v)	31.184 mg	*
	galantamine hydrobromide	2.563 mg (2 mg galantamine base)	
	HPMC 2910 5 mPa.s and PEG 400	4.229 mg (Opadry OY-7240 Clear)	
15	purified water	89.321 µl	*
	capsules size nr. 4, 2, 1 and 0.		

*: these ingredients do not occur in the end product

20 *Preparation :*

a) Drug coat solution

Galantamine hydrobromide and Opadry OY-7240 Clear were dissolved in purified water at room temperature.

25 b) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, HPMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

c) Drug topcoat solution

30 Galantamine hydrobromide and Opadry™ OY-7240 Clear were dissolved in purified water at room temperature.

d) Coating process

35 A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug coat solution was sprayed on the

spheres moving in the apparatus. When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The release rate controlling membrane coat solution was sprayed on the spheres moving in the apparatus. After drying for about 2 minutes, the controlled release membrane coated spheres were sprayed with the drug topcoat solution. After drying for about 2 minutes, the topcoated spheres were allowed to cool to room temperature, sieved and were filled into a stainless steel drum.

e) capsule filling

The topcoated spheres (96.841 mg ; 193.683 mg ; 290.524 ; 387.365 mg) were filled into hard-gelatin capsules (size numbers 4, 2, 1, 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg, Germany) yielding oral capsules containing respectively 8 mg, 16 mg, 24 mg and 32 mg galantamine base.

Example 6 : galantamine oral capsules (F9)
(75 % CR pellets and 25 % IR topcoat)

Spheres having slightly faster release were made by lowering the ratio of ethylcellulose 20 mPa.s to HPMC 2910 5 mPa.s to 72.5 : 27.5 (as compared to the ratio 75 : 25 in the previous example.

Example 7 : In vitro dissolution of the topcoated spheres

Comparative *in-vitro* dissolutions studies were performed on the topcoated spheres formulations F5 to F8 and F9. The medium was 500 ml of USP buffer pH 6.8 at 37°C in Apparatus 2 (USP 23, <711> Dissolution, pp. 1791-1793) (paddle, 50 rpm).

The following results were obtained :

F5 to F8

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	32.20	30.44	37.47	30.44	30.44	38.05	33.17
120	42.54	41.37	48.39	41.37	42.54	42.54	43.13
240	58.93	60.10	65.96	61.27	61.27	61.27	61.47
480	85.47	80.20	84.30	81.96	81.37	80.79	82.35
720	91.52	90.35	97.37	99.13	92.11	87.42	92.98
1080	96.59	97.18	102.45	102.45	99.52	98.94	99.52
1410	96.40	97.57	103.42	103.42	100.5	101.08	100.40

F9

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	38.9	36.0	36.5	39.5	33.4	37.2	32.86
120	60.3	55.7	56.9	60.4	60.9	55.1	58.2
240	89.5	81.8	86.2	86.7	91.2	84.0	86.6
480	103.4	103.6	95.9	101.7	100.8	105.8	101.9
720	107.0	99.0	104.0	103.1	109.1	100.8	103.8

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Claims

1. A controlled release formulation containing galantamine as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating.
2. A formulation according to claim 1 wherein galantamine is in the form of galantamine hydrobromide (1:1).
3. A formulation according to claim 1 wherein the water soluble excipient is a film forming polymer.
4. A formulation according to claim 3 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.
5. A formulation according to claim 4 wherein the water soluble polymer is selected from the group comprising
- alkylcelluloses such as methylcellulose,
 - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
 - hydroxypropylcellulose and hydroxybutylcellulose,
 - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
 - carboxyalkylcelluloses such as carboxymethylcellulose,
 - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
 - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
 - carboxyalkylcellulose esters,
 - starches,
 - pectines such as sodium carboxymethylamylopectine,
 - chitine derivates such as chitosan,
 - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,

- polyacrylic acids and the salts thereof,
 - polymethacrylic acids and the salts thereof, methacrylate copolymers,
 - polyvinylalcohol,
 - polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
 - 5 - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and
copolymers of ethylene oxide and propylene oxide.
6. A formulation according to claim 5 wherein the water soluble polymer is
hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.
- 10 7. A formulation according to claim 6 wherein the weight-by-weight ratio of
hydroxypropyl methylcellulose HPMC 2910 5 mPa.s to galantamine is in the range
of 17 : 1 to 1 : 5.
- 15 8. A formulation according to claim 2 wherein galantamine hydrobromide (1:1) and
the water soluble, film forming polymer are layered or coated on an inert sphere.
9. A formulation according to claim 8 wherein the inert spheres are 16-60 mesh
(1,180-250 • m) sugar spheres (NF XVII, page 1989).
- 20 10. A formulation according to claim 1 wherein the release rate controlling membrane
coating comprises a water insoluble polymer and optionally a plasticizer.
11. A formulation according to claim 10 wherein the water insoluble polymer is
25 ethylcellulose and the plasticizer is selected from the group comprising dibutyl
sebacate, diethyl phthalate and triethyl citrate.
12. A formulation according to claim 11 wherein the weight of the release rate
controlling membrane coating ranges from 3 % to 15 % of the uncoated particle.
- 30 13. A formulation according to claim 1 wherein a seal coat lies between the drug core
and the release rate controlling membrane coating.
14. A formulation according to any one of claims 1 to 13 further comprising a topcoat
35 comprising galantamine and water-soluble polymer.
15. A formulation according to claim 14 capable of releasing in USP buffer pH 6.8 at
37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50

rpm) from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours

- 5 16. A dosage form comprising a therapeutically effective amount of the controlled release formulation of any of claims 1 to 15.
- 10 17. A dosage form according to claim 16 which delivers a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.
18. A dosage form according to claim 16 wherein part of the galantamine is present in an immediate release form.
- 15 19. A dosage form according to claim 18 wherein said immediate release form comprises particles as described in claim 1 lacking the release rate controlling membrane.
- 20 20. A dosage form according to claim 18 wherein said immediate release form comprises immediate release minitabets.
21. A dosage form according to claim 18 wherein said immediate release form comprises a controlled release formulation of claim 14.
- 25 22. A dosage form according to claim 16 providing a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.
- 30 23. A pharmaceutical package suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.
- 35 24. A pharmaceutical package as claimed in claim 23 adapted for titrating a patient who is 'acetylcholine esterase inhibitor'-naïve, characterized in that said package comprises 21-35 daily sequential dosage units of
- (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
- (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,

- (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
- (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.

5

25. A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is 'acetylcholine esterase inhibitor'-tolerant, characterized in that said package comprises daily dosage units comprising from 15 to 30 mg galantamine.
- 10 26. A process of preparing a formulation according to claim 1 comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.
- 15 27. A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being
- 20 sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.
28. A method according to claim 27 wherein the related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation,
- 25 bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit, hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.
29. A method according to claim 27 wherein the adverse effects belong to the group
- 30 comprising nausea, vomiting, sweating, restlessness, and insomnia.

T09220 1658860

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

John Paul MCGEE; Paul Marie Victor GILIS;
 Marc Maurice Germain DE WEER; Valentin
 Florent Victor de CONDE; Herman Johannes
 Catherina de BRUIJN and, Frederic Anne Rodolf
 VAN DYCKE
 International Application No. : PCT/EP99/10257

Group Art Unit: Not yet known

Examiner: Not yet assigned

International Filing Date: 20 December 1999

For: CONTROLLED RELEASE
 GALANTAMINE COMPOSITION

Assistant Commissioner for Patents
 Washington DC 20231

Sir:

ASSOCIATE POWER OF ATTORNEY

The undersigned, of the firm WOODCOCK WASHBURN KURTZ
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Dianne B. Elderkin	Registration No. 28,598	Anthony J. Rossi	Registration No. 24,053
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Henrik D. Parker	Registration No. 31,863	Michael J. Swope	Registration No. 38,041
Suzanne E. Miller	Registration No. 32,279	Michael J. Bonella	Registration No. 41,628
Lynn B. Morreale	Registration No. 32,842	Harold H. Fullmer	Registration No. 42,560
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Michael D. Stein	Registration No. 34,734	Chad Ziegler	Registration No. 44,273
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Steven D. Maslowski	Registration No. 46,905
S. Maurice Valla	Registration No. 43,966
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Robin S. Quartin	Registration No. 45,028
Patrick J. Farley	Registration No. 42,524
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Emma R. Dailey	Registration No. P48,491
Stephen C. Timmins	Registration No. P48,481
Erich M. Falke	Registration No. P49,049
Jane Smith Ingelese	Registration No. P48,444

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

John Paul MCGEE; Paul Marie Victor GILIS;
 Marc Maurice Germain DE WEER; Valentin
 Florent Victor de CONDE; Herman Johannes
 Catherina de BRUIJN and, Frederic Anne Rodolf
 VAN DYCKE
International Application No. : PCT/EP99/10257

Group Art Unit: Not yet known

Examiner: Not yet assigned

International Filing Date: 20 December 1999

For: CONTROLLED RELEASE
 GALANTAMINE COMPOSITION

Assistant Commissioner for Patents
 Washington DC 20231

Sir:

ASSOCIATE POWER OF ATTORNEY

The undersigned, Mary A. Appollina, Registration No. 34,087, of **Johnson & Johnson**, One Johnson Plaza, New Brunswick, N.J. 08933-7002, hereby appoints the following of the firm **WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP**, One Liberty Place - 46th Floor, Philadelphia, Pennsylvania 19103, Attorney and/or Agents for Applicant(s):

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Barbara L. Mullin	Registration No. <u>38,250</u>	David N. Farsiou	Registration No. <u>44,104</u>

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Stephen C. Timmins	Registration No. <u>P48,481</u>
Erich M. Falke	Registration No. <u>P49,049</u>
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Date: *July 11, 2001*

Mary A. Appollina
 Mary A. Appollina
 Registration No. 34,087
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) <input checked="" type="checkbox"/> Declaration Submitted with Initial Filing OR <input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)	Attorney Docket Number	JAB 1461-PCT-USA
	First Named Inventor	McGee, John Paul
	COMPLETE IF KNOWN	
	Application Number	/
	Filing Date	
	Group Art Unit	
	Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CONTROLLED RELEASE GALANTAMINE COMPOSITION

the specification of which

☐ is attached hereto
OR

☒ was filed on (MM/DD/YYYY) 12/24/1998 as United States Application Number or PCT International

Application Number PCT/EP99/10257 and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
98204447.1	E.P.	12/24/1998	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
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Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

[Page 1 of 4]

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

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Name	Registration Number	Name	Registration Number
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Andrea L. Colby	30,194	Mary A. Appollina	34,087

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

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☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

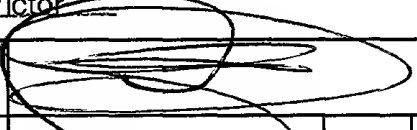
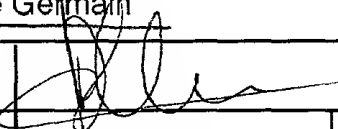
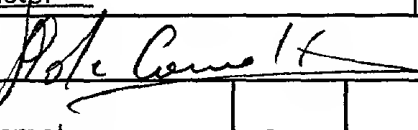
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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 3 of 4

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
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ADDITIONAL INVENTOR(S) Supplemental Sheet Page 4 of 4

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Inventor's
Signature

Date

Residence: City

State

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City

State

ZIP

Country

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